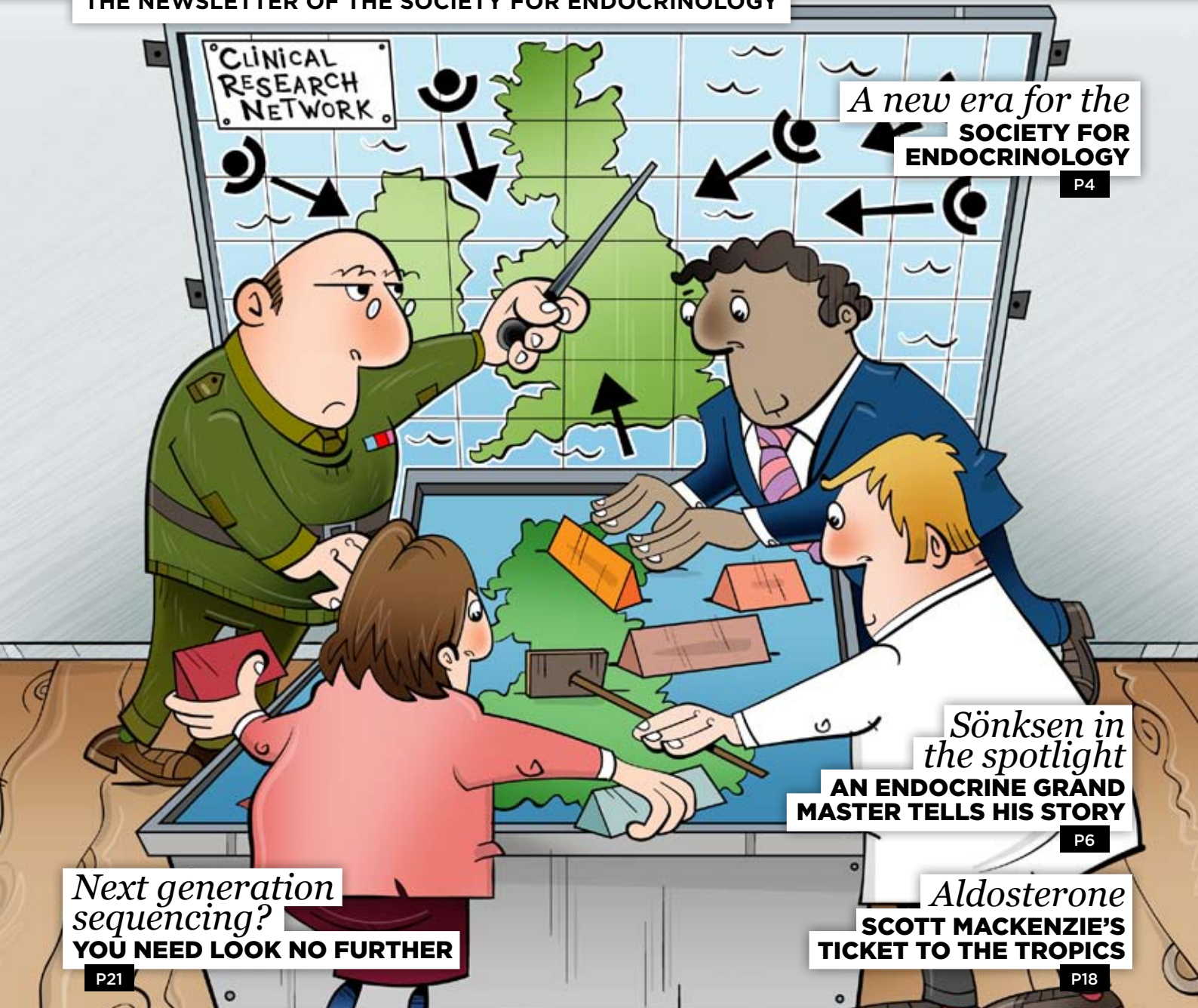


# THE ENDOCRINOLOGIST

THE NEWSLETTER OF THE SOCIETY FOR ENDOCRINOLOGY



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**SOCIETY FOR  
ENDOCRINOLOGY**

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## A WORD FROM THE EDITOR...



I am very flattered to have been asked to take over as editor of *The Endocrinologist* and hope I can justify my selection. My friends now think I am the editor of a high-brow scientific journal and I will keep it a secret from them that it is actually a magazine fit for the last slot on 'Have I Got News for You!' I have no idea how many people genuinely take the time to read this newsletter, but I am taking a wild guess that you are one of them. My feeling is that this newsletter should be an all-encompassing quarterly update of what is happening clinically, scientifically and politically within our specialty, with something of the human angle behind our endocrine world. One thing I have been pleased to introduce is the series of interviews with influential endocrinologists of our generation.

To match the Society's snazzy new identity, we have a new newsletter design (I think I can feel your excitement), and we have appointed a team of scientists and clinicians to join the editorial committee. We are very reliant on you to provide us with new ideas and original articles, and this newsletter presents a refreshing chance for you to give an entirely biased, non-evidence based opinion on a particular aspect of endocrinology which is dear to your heart. It is also a chance to showcase our subject to the lay public, who might happen upon this publication whilst at the hairdressers or when rummaging through the recycling bin. In all seriousness, although it is a tricky time for our specialty in terms of funding for research and the uncertainties around commissioning, endocrinology remains the most interesting specialty by far, and we should be shouting it from the rooftops (or at least from the pages of this newsletter if you can't get up on the roof). I hope you enjoy this current edition, which has a lot of stuff in it!

BEST WISHES  
MILES LEVY

Editor: Dr Miles Levy  
Associate Editor: Dr Tony Coll  
Commissioning: Tracey Curtis  
Coordination: Andrew Lowe  
Sub-editing: Caroline Brewer  
Design: Third Floor Design

**Society for Endocrinology**  
22 Apex Court, Woodlands,  
Bradley Stoke, Bristol BS32 4JT, UK  
Tel: 01454 642200  
Email: info@endocrinology.org  
Web: www.endocrinology.org  
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#### THE ENDOCRINOLOGIST NEWSLETTER ENQUIRIES

Jennie Evans  
Public & Media Relations Manager.  
Email: jennie.evans@endocrinology.org  
Tel: 01454 642230

#### 2013 ADVERTISING

Please contact  
advertising@endocrinology.org

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You can view this issue online:  
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## Become a contributor...

Contact the Editorial office at [info@endocrinology.org](mailto:info@endocrinology.org)

The Society welcomes contributions and article suggestions; contact the Editorial office at [info@endocrinology.org](mailto:info@endocrinology.org)  
Deadline for news items for the Summer 2013 issue: 8 March 2013. Deadline for news items for the Autumn 2013 issue: 17 July 2013.

## SOCIETY BES 2013: SPRINGTIME IN HARROGATE

Register now for the UK's premier scientific meeting on hormone research! The Society for Endocrinology BES conference takes place in Harrogate on 18-21 March 2013.

This 4-day meeting will encompass the best in British and international basic science and translational research, clinical investigation and clinical practice in endocrinology. It is an unrivalled opportunity to network with endocrinologists from across the globe.

You will enjoy 8 plenary lectures from world-renowned researchers, including Ronald Evans (USA), Fernand Labrie (Canada) and Anna Spada (Italy), as well as 12 symposia covering a range of translational topics. Education workshops are an exciting addition to the programme for 2013.

## NEW PRESIDENT

We are delighted to announce that the Society's next President will be Professor Steve O'Rahilly from the University of Cambridge. He will be officially elected at the AGM in Harrogate during the Society BES 2013 meeting and will take up office at the 2014 AGM.

## SOCIETY FOR ENDOCRINOLOGY BES 2013

Oral communication sessions will feature, along with a large poster display and exhibition. Tailored sessions will cater to the needs of nurses, and the highly popular Young Endocrinologists' symposium will provide advice on having a successful research career. In addition, you will have the chance to 'Meet the Expert' at sessions for both clinicians and basic scientists.

To find out more, to register, or to view the full programme, see [www.endocrinology.org/meetings/2013/sfebes2013](http://www.endocrinology.org/meetings/2013/sfebes2013). Follow #sfebes13 on Twitter for the latest news and views from the meeting.

We look forward to welcoming you all to Harrogate!



## MEDALLISTS FOR 2014

The Society is pleased to announce the following medallists, who will speak at the Society BES 2014 meeting in Liverpool.

**Dale Medal**  
Bert O'Malley, Baylor College,  
Houston, TX, USA

**Transatlantic Medal**  
Mitchell Lazar, University of  
Pennsylvania, PA, USA

**Society for Endocrinology Medal**  
Andrew Loudon, University of  
Manchester, UK

**European Medal**  
Theo Visser, Erasmus University,  
Rotterdam, The Netherlands

**Hoffenberg International Medal**  
Robert I McLachlan, Prince  
Henry's Institute, Clayton, Victoria,  
Australia

## ALAN BLACKSHAW

We are sorry to announce the death of Senior Member Dr Alan Blackshaw of Indooroopilly, Queensland, Australia.

## CONGRATULATIONS

Iffy Middleton of the Gender Identity Clinic, London, has been presented with an NHS Hero Award and a Trust Quality Award under the category of 'Caring'. The awards were assigned after a vote by patients, many of whom attend her nurse-led clinic.

## ANNUAL REPORT AND AGM

With this mailing you will find your copy of the Annual Report. This gives a snapshot of the activities we have undertaken in the last financial year. Come to the AGM at the Society BES 2013 meeting in Harrogate to learn more. The AGM will be held on Wednesday 20 March in the Main Auditorium of Harrogate International Centre.

## CALL FOR NOMINATIONS! COMMITTEE MEMBERS NEEDED

Vacancies on the following committees will arise at the end of 2013. If you would like to be involved in running your Society, please consider standing for election to the:

Clinical Committee  
Corporate Liaison Board  
Finance Committee  
Nominations Committee  
Nurse Committee  
Programme Committee  
Science Committee  
YE Steering Group

Full details and nomination forms are available on the specific committee pages at [www.endocrinology.org/about/committee.html](http://www.endocrinology.org/about/committee.html).

## CORPORATE SUPPORTERS 2013

We are pleased to announce the Society's Corporate Supporters for 2013. Many of the Society's activities are facilitated with the help of these organisations, and we would like to thank them all for their continued assistance. Companies wishing to participate in the scheme should contact Amanda Helm in the Bristol office ([amanda.helm@endocrinology.org](mailto:amanda.helm@endocrinology.org)).

Platinum supporters:  
Ipsen Ltd  
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Gold supporters:  
Bayer HealthCare  
Ferring Pharmaceuticals Ltd  
Merck Serono  
Novartis Pharmaceuticals UK Ltd  
Novo Nordisk Ltd  
ProStrakan  
ViroPharma

Silver supporter:  
Sandoz Ltd

## SOCIETY CALENDAR

18-21 March 2013  
**BES 2013**  
Harrogate

16 May 2013  
**REGIONAL CLINICAL CASES**  
Newport

16-17 September 2013  
**ENDOCRINE NURSE UPDATE**  
Stratford-upon-Avon

18-20 October 2013  
**CAREER DEVELOPMENT WORKSHOP & FELLOWSHIP TRAINING DAY**  
Oxfordshire

4-6 November 2013  
**CLINICAL UPDATE**  
Bristol

24-27 March 2014  
**BES 2014**  
Liverpool

see  
[www.endocrinology.org/meetings](http://www.endocrinology.org/meetings) for full details

## GRANT AND PRIZE DEADLINES 2013

11 March  
**SUMMER STUDENTSHIP**

15 April  
**CONFERENCE GRANT**

27 May  
**EARLY CAREER GRANT**

15 July  
**UNDERGRADUATE ACHIEVEMENT AWARD**

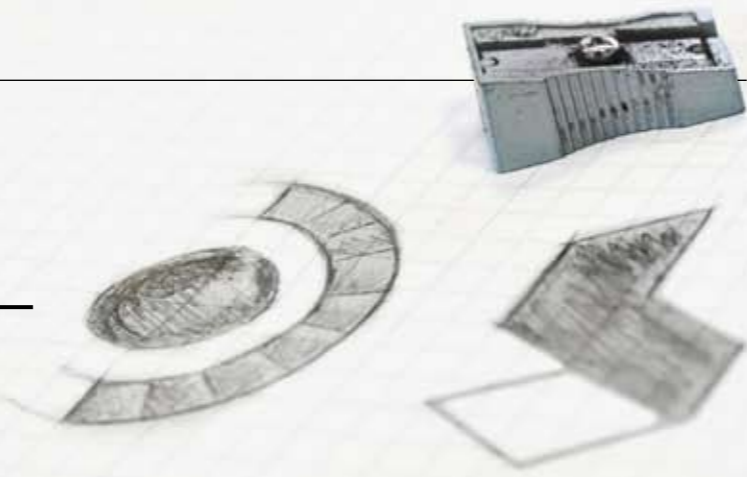
15 August  
**CONFERENCE GRANT**

27 November  
**EARLY CAREER GRANT**

15 December  
**CONFERENCE GRANT**

see  
[www.endocrinology.org](http://www.endocrinology.org)  
for full details

## A NEW ERA FOR THE SOCIETY FOR ENDOCRINOLOGY



The Society for Endocrinology is the only UK charity dedicated to representing endocrinology. To ensure we provide the best service to the endocrine community, we need to position ourselves to meet the increasing needs of our members and the public over the next 10 years, in the UK and globally, as our speciality develops.

So during 2011 (with help from our members), staff at the Society's Bristol office worked hard to develop our strategic plan.

### WHAT WE'VE BEEN WORKING ON

Our first step was to research people's perceptions of the Society for Endocrinology, to evaluate whether there was a need for change. We conducted lengthy research, focus groups, workshops and interviews with a cross-section of people connected to the Society, including clinicians, scientists, nurses, trainee members, patient groups and members of the general public. From here, we examined where the Society should be positioned – what we wanted to be recognised for and the impact of our work to be. An independent specialist examined the evidence and worked with us to develop recommendations to take the Society forward. This was reviewed and agreed in early autumn by the Society's Officers and Head Office Leadership Team.

### OUR FINDINGS

Generally, we found the Society was in good shape, but there were a couple of areas that needed fine-tuning. We found there was *confusion* over the relationship between the Society and its trading company Bioscientifica, *conflict* between the Society as a charity and Bioscientifica as a not-for-profit organisation and *uncertainty* about the future.

The recommendations were to clarify the relationship between the two organisations and magnify their very distinct characteristics. Everything we do will be based around three fundamental principles: **engage, support, advance**.

We are working towards becoming an organisation that delivers even more benefit to the endocrine community, to be a society of which you can be even prouder to be a member.

### ENGAGE

Connect and communicate with our membership and beyond, creating a vibrant community, encouraging more people into the discipline and building productive partnerships across the sector

### SUPPORT

Our core role is to support all our members and the discipline of endocrinology by providing an unparalleled suite of grants, training programmes and learning resources to help our members further their individual careers

### ADVANCE

Our end goal is to advance scientific and clinical endocrine education and research to improve public health and knowledge

Two key features of this plan are (a) to maximise appeal and value to members and potential members, and (b) to be a central information gateway for hormone information and knowledge resources. To achieve this, we need to be at the forefront of the sector, which means increasing recognition of the Society, making it easier for different groups to connect with us, developing access to our services, and maximising our support, advocacy and funding streams to you, our members.

### HOW WILL IT AFFECT OUR WORK AS A SOCIETY?

Our vision, goals and charitable remit remain unchanged. However, what will change is how we go about delivering this vision. This change is not just about a new identity. It is our organisational promise that we will strive to engage, support and advance the discipline of endocrinology. These values will shine through in everything we do, focusing our activities, resources and the way we communicate.

### COMMUNICATING OUR NEW IDENTITY

As you may have already seen, from the end of January, we started communicating about our new identity (our values and promises). This is just the beginning; we have more plans in place to continue the dialogue. You will see more in the coming months, especially at the Society for Endocrinology BES 2013, where we will showcase the new values and identity.

*'Research in endocrinology has come on in leaps and bounds over the past decade. To ensure that this progress continues through the next 10 years ... I support this new identity for the Society, because it offers us an exciting opportunity to propel the discipline into the stratosphere so we can realise our potential.'*

PROFESSOR ASHLEY GROSSMAN,  
PRESIDENT, SOCIETY FOR ENDOCRINOLOGY



We hope you love the new designs for your journals, which bring them together as a recognisable family of publications while still maintaining each journal's individual focus and reputation for publishing high quality, cutting-edge research.

*'Our aim is to ensure the Society for Endocrinology is in a strong position to meet the increasing needs of our members and the public in line with our strategic plans over the next 10 years. Our new values give us the persona and the tools to increase our reach and profile, boosting our support and representation to members while also attracting others into the discipline.'*

LEON HEWARD-MILLS, CHIEF EXECUTIVE,  
SOCIETY FOR ENDOCRINOLOGY

### YOUR TRADING COMPANY - BIOSCIENTIFICA

As many of you know, the Society's trading company Bioscientifica offers a range of commercial services to learned societies, the academic sector and the pharmaceutical industry. What some of you may not know is the importance of Bioscientifica's success in funding our charitable activities, through Gift Aiding all its profits to the Society.

As part of this project, we also reviewed Bioscientifica's strategy and identity. Their growth is vital for your Society, to provide the financial support needed to continue to deliver its aims. Bioscientifica and the Society have a shared purpose to 'improve knowledge, health and life'.

Find out more about Bioscientifica's new identity and services at [www.bioscientifica.com](http://www.bioscientifica.com)



### OUR INVESTMENT

For us to continue to grow and support the endocrine community effectively, we need to invest in our organisation, communicating accurately what we stand for, what we do and how we change things for the better. Although this work means committing to initial costs, this will be more than offset by the measurable benefits that the Society and the discipline as a whole will reap. During the 2012/13 financial year we expect to spend in the region of £50 000 on this project, representing 1.9% of the total planned Society spend. It will not impact on our grants programme or on other planned activities. We have carried out extensive research on the costs and benefits of this exercise, and would not commit the money unless we felt that it would be demonstratively beneficial for the organisation as a whole.

*'As a member, I was encouraged by the lengths the Society went to, to ensure that the members' views were paramount to their developments. Having been a part of the research I can clearly see that the feedback has been considered and the new identity really does capture the essence of endocrinology, helping to define the role of Bioscientifica more clearly to me as a member and bringing in a strategy to promote popular understanding of hormones amongst the public.'*

PROFESSOR JOHN WASS, PAST CHAIRMAN,  
SOCIETY FOR ENDOCRINOLOGY

### OUR PROFILE WITH THE PUBLIC

So far, we have concentrated on how we can work with and support members of the endocrine community who have already specialised in the discipline. However, we also recognise there is a much larger conversation we need to have with non-specialists and the general public, to raise awareness and knowledge of hormones and hormone-related conditions, and to ensure that unreliable information can be challenged. Work on this is underway and we will bring you more details soon.

### OUR NEW LOGO

The Society's new logo represents a stylised version of a hormone and receptor. The change in colour of the receptor from top to bottom signifies its action. The colours are designed to be bold and stand out from the crowd, allowing us to be instantly recognisable, whilst still giving us the authority to forward the views of the Society as a professional body.



### STRATEGY

The Society performs many different activities, but at the core of all of these are you, our members. Having such valuable expertise on our side, we are in a unique position to act as an advocate for endocrinology and support endocrinologists throughout their careers.

For more information on our strategic plan, visit [www.endocrinology.org](http://www.endocrinology.org)



### WHAT NEXT?

We want to hear your views, what you would like the Society for Endocrinology to do for you, and how you would like to get involved in our work.

Email us at [members@endocrinology.org](mailto:members@endocrinology.org)  
Call us at 01454 642200  
Contact us via Facebook or Twitter

[facebook.com/SocietyforEndocrinology](https://www.facebook.com/SocietyforEndocrinology)

[twitter.com/Soc\\_Endo](https://twitter.com/Soc_Endo)

We look forward to hearing your thoughts

## AN INTERVIEW WITH... PETER SÖNKSEN

INTERVIEW BY MILES LEVY



When I went down to meet Peter Sönksen, I was pleasantly surprised to find a ruddy and healthy looking chap, appearing rather younger than his 76 years. I knew he had been in a bad skiing accident rendering him a wheelchair user, the result of a fairly blameless attempt to ski back home after a day's excursion in Utah. He came across an unexpected 10 foot drop, landed on his feet and fell forwards, hyperextending his neck. Lying face down in the snow he was unable to move his arms or legs, but luckily could breath and speak.

This rather spoilt his plans to spend his retirement flitting between the UK and the US skiing, sailing and playing golf. Despite this major setback, the steely look in his eyes suggests he still has a lot more planned to achieve in his life.

### GETTING INTO MEDICINE AND RESEARCH

Peter was born in Germany in 1936. The family fled to England when his father fell foul of the Nazis after an alleged money-laundering event. Within a few months of settling in Kent, his father was tragically killed in a road traffic accident. Subsequently his mother brought him up single-handedly, working as a housekeeper and then as a dressmaker.

Sönksen was accepted as a boarder at St Bartholomew's Grammar School in Newbury. He excelled academically and, at 6 foot 5 inches tall, was a useful second row at rugby. No one in the family was medical, and he is not quite sure why he became a doctor, although he recalls a nurturing side whilst tending wild creatures at his rural home. He was accepted at the Middlesex Hospital in London, where his career was moulded. Going from a quiet rural boarding school to London was 'terrifying ... there were girls everywhere ... lots of beer and sport ... and a lot of playing cards!'

A key figure in Sönksen's life was the late Sir John Nabarro, consultant endocrinologist at the Middlesex Hospital. Peter was Nabarro's House Officer at the Middlesex. After passing the MRCP, he fancied having a stab at research 'rather than just playing cards'. He applied for a haematology project involving intravenous influenza vaccine injection in splenectomised patients, which in the end did not receive ethical approval. Sönksen had injected himself and his supervisor intravenously with the vaccine, resulting in a dreadful dose of 'flu over the next 24 hours but, as he comments, he has never had it since!

Nabarro discovered that Peter was out of a job and rang him up whilst he was working as a GP locum: 'Sönksen, the girl who was doing research with the rats has developed an allergy to them ... do you want her job?' Peter took the post and never looked back.

He found himself well-suited to research: 'a treasure hunt for new things'. His MD was on the correlation between bioassays and immunoassay for insulin. He became interested in hormonal action, particularly of insulin and GH, and found a significant difference between insulin action in acromegalic patients compared with normal individuals.<sup>1</sup> This set the theme for Sönksen's academic career.

### THE REGISTRAR YEARS

In 1967 Peter went to Boston, MA, USA, having won a Harkness Scholarship, and worked at Harvard Medical School. In those days a 'BTA' (Been To America) carried a high premium for career progression. Whilst at Harvard, Peter investigated the metabolism of GH and insulin in dogs and man. He met an ambitious young medic called George Alberti, and taught him how to do immunoassays.

Professor Dame Sheila Sherlock (the infamous hepatologist from the Royal Free) summoned Sönksen to New York to have breakfast with her. She had heard he was a rising star (and had won an RCP Scholarship) and promised him a laboratory to carry on his academic endocrine pursuits back in London. Nabarro felt it would be a good career move and endorsed it. However, on his arrival in London, Sönksen discovered a dusty laboratory and that Sherlock 'seemed to have forgotten all about it'. With no money or grant, Peter resigned after 2 weeks, returning 'home' to Nabarro and the Middlesex Hospital. By the look on Sönksen's face, one suspects that not many people have the nerve to resign from a Sheila Sherlock post and survive!

Whilst Senior Registrar at the Central Middlesex, Peter was asked to keep an eye on his consultant. A known manic depressive, tragically he was soon to take a dose of cyanide. Sönksen successfully resuscitated him, but after a prolonged spell on ITU he died. It was under these unhappy circumstances that Peter took over as a consultant locum within 3 months of becoming Senior Registrar, though he reflects that he 'could finally pay the bills' as a result of his sudden pay rise.

Sönksen was appointed Senior Lecturer in Medicine at St Thomas' Hospital in 1971. He admits, 'I never thought they appointed people from north of the river, let alone grammar school boys, but I was quite wrong'. 'Tommy's' was desperate for a talented consultant diabetologist, as a series of clinical disasters had followed a decision taken 4 years earlier that they did not need any diabetes specialists! Peter created the current St Thomas' Diabetes and Endocrine Department, establishing close links with chemical pathology, and participating in the general medicine service and acute take until he was 60.

### SEMINAL CONTRIBUTORS TO DIABETES

In the 1970s, diabetic ketoacidosis (DKA) was treated initially with 100 Units of insulin both intravenously and intramuscularly, the assumption being that reduced peripheral uptake of glucose was the predominant problem in type 1 diabetes. Sönksen showed that much lower doses of infused insulin were sufficient to correct the hyperglycaemia and acidosis. The results were so striking that the clinical trial he had organised was stopped early, and low dose insulin infusions remain the treatment for DKA.<sup>2</sup>

*"He was so impressed with his hospital-based diabetes specialist nurse that he married her!"*

Peter really found himself on fertile ground at a very exciting time. He felt strongly that it was important to study both diabetes and endocrinology. To the chagrin of the indomitable matrons at St Thomas', Peter decided that nurses as well as doctors should play an important role in research and community- and hospital-based diabetes. Peter employed the first ever hospital-based diabetes specialist nurse (DSN), having previously successfully established two community-based DSNs in Lambeth. He was so impressed with his hospital-based DSN that he married her! 'I've not done too badly there,' he tells me with a glint in his eye, and with this look it is clear that she has been a pillar of support to him.

Sönksen was ahead of his time with computers. Through a skiing friend who worked for IBM he learnt to program in Fortran, which started a long and difficult relationship with computers and a project aiming to set up computerised diabetes clinic records. In the early days, Peter would cycle to Imperial College with a stack of punch-coded cards bound by a rubber band and feed them into a primaeval computer. Through 'sheer perseverance' Sönksen secured a British Diabetic Association (now Diabetes UK) grant, leading eventually to the first diabetes database (DIABETA),<sup>3</sup> and subsequently to a massive EU-funded project known as EURODIABETA ('hell on earth!').<sup>4</sup>

*"He is most proud of his 1978 BMJ article, showing the key role of insulin in inhibiting hepatic glucose output, proteolysis and ketone formation in type 1 diabetes"*

Sönksen investigated dynamic aspects of metabolic diseases and actions of insulin and insulin analogues using isotope studies. He discovered that the hyperglycaemia of diabetes was due to excess hepatic glucose production rather than reduced uptake into the periphery, an entirely new concept at the time. Sönksen's studies confirmed Starling's 1916 hypothesis that the pancreas produces a 'chalone' substance which inhibits glucose production by the liver.<sup>5</sup> He is most proud of his 1978 *British Medical Journal* article,<sup>6</sup> showing the key role of insulin in inhibiting hepatic glucose output, proteolysis and ketone formation in type 1 diabetes.

CONTINUED ON PAGE 8...

### DEAR PROFESSOR SÖNKSEN...

These are just some of the testimonials gathered by Peter Sönksen from recipients of GH treatment and their families

*"Prior to starting rhGH I had very little energy or strength. I had trouble coping with everyday life. Since starting the treatment my life has changed beyond belief. Very little phases me now, I have so much more energy. Even my hair has thickened up and is now 'normal'. I now have a real zest for life."*

*"Although treatment for my macroprolactinoma put me back on my feet, the rhGH provided me with an extra capacity for stamina, i.e. on my daily cycle commuter journey I have become quicker and can sustain a longer hard push. There is no doubt in my mind that it has made a difference."*

*"Prior to GH treatment, I lacked energy and had little stamina for physical activity over long periods. My weight was gradually increasing, my complexion was pale and body hair was sparse (even though prescribed testosterone). I was mildly depressed. At the end of the first year's treatment, I noted a change in shape as I lost trunk fat (less 24%) and gained muscle (additional 11%). I also developed more energy, alertness and strength and seemed to gain extra manual dexterity, e.g. when dialling the phone. My sexual libido and orgasms also improved, which was completely unexpected, and body hair, previously sparse, became more profuse. My wife and sons independently noted the increase in physical strength and energy, and as a family they feel that GH has improved the quality of life. My sons were approaching manhood at this time (aged 17 and 21 years), and my wife feels that it was helpful and important for them to relate to a father who was more masculine in shape and physical action."*

## AN INTERVIEW WITH... PETER SÖNKSEN

CONTINUED FROM PAGE 7

In the 1970s, glucose measurements were done using large non-portable devices. A pregnant patient with type 1 diabetes confined to hospital demanded to know why she couldn't borrow the meter and measure her own sugars at home. This she did with great success, so ending the need to hospitalise patients for the last 3 months of pregnancy. Peter discussed this predicament with an engineer-patient in clinic, who developed the first prototype for a portable glucometer (Glucochek). Sönksen was also first to introduce immediate HbA1c results 'online' in clinic with the assistance of a research fellow and an array of mini-columns made from plastic syringes.<sup>7</sup>

### THE START OF GROWTH HORMONE IN ADULTS

In 1987, Peter was rung by a senior employee of Pharmacia about the role of GH in adults. Cadaveric GH could cause Creutzfeldt-Jakob disease, which necessitated the development of recombinant GH (rGH). The company were looking for indications for its use outside children (although Sönksen did not know this at the time). Peter asked his research fellow, Franco Salomon, to review what was known about the physiological effects of GH in adults. This was long before any adults had received rGH, so it was an entirely new concept greeted with scepticism by some eminent endocrinologists. The review was presented at a paediatric symposium in Vienna, which was shortly followed by a Pharmacia-sponsored randomised controlled trial.<sup>8</sup> The effects of rGH on body composition and metabolism in adults with GH deficiency led to a *New England Journal of Medicine* publication that has been cited over 1000 times (Sönksen's most quoted paper).<sup>9</sup>

Sönksen is in no doubt that most GH-naïve patients had a genuine, dramatic response in terms of general well-being. In preparing supporting material for NICE's review of GH treatment in adults, many of his patients sent him personal anecdotes on how much better they felt. Peter comments, 'I've got around 75 of these, which are very interesting and ought to be published in some way.' Several are reproduced towards the end of this article (page 8-9).

Sönksen led the way for all things adult GH-related, and was elected as the first President of the Growth Hormone Research Society after it was formed in 1990.

The next phase of Sönksen's career began with a phone call whilst on a ward round in 1993. GH had become a major drug of abuse in sport, and the International Olympic Committee (IOC) 'were hungry for information' on how to detect it. After a while persuading the IOC that research was needed to develop a test, Sönksen led an EU- and IOC-funded international academic group investigating markers of GH action, including IGF-1, osteocalcin, pro-collagen (P-III-NP), IGFBP's and many others.

With \$2 million per year for 3 years, the group achieved their objective. Using IGF-1 and P-III-NP, a formula was created that had reasonable sensitivity in detecting GH administration in the preceding 2 weeks, at a false positive rate of 1 in 10000. The method was approved by an external panel during an IOC workshop in 1999, with some refinement recommended to close legal loopholes.

'The President of the IOC authorised a further grant of \$1 million to complete installation of the method, but funding was suddenly withdrawn by the Medical Commission Chairman before a contract was signed. No reason was given.' Sönksen paints a picture of the IOC as a shady network, steeped in politics and foul play (although the current President, orthopaedic surgeon Jacques Rogge, seems to have broken the mould and come out of it as a decent upstanding individual).

*"I now live a full life, my energy levels are high, according to my wife, in line with the way I behaved before the problem started. My physique is back to normal whereas before the treatment no amount of diet[ing], or the little exercise I could take, would get rid of what was like an all over layer of fat. I am not aware of any side effects at all. I consider the treatment to have been tremendously successful. I think it should be available to any person that needs it. I do feel that without medical prompting, those in need of it, like myself, slip into a condition of not being aware of the deterioration that has occurred. I would like to thank you and all of your team for what you have done for me."*

*"GH, without doubt, has been Richard's salvation. Since it was first prescribed in the early 1990s, he has become again a fit and active person, easily coping with his demanding life. I have not noticed any side effects in him using GH and I regard its use, for him, to be wholly beneficial."*

*"I cannot remember the exact date that I started on GH, but I do know that I began to feel better – not earth-shatteringly so, but in some indefinable way which I am unable to explain, and things became so much easier to cope with. I had and still have more energy than in the dark '60s and '70s and feel that I would probably still be more agile now if it were not for a very painful lower back – I have had extensive treatment for this but now just take painkillers. Apart from my back I feel fit and well and it is great. I can cope with daily life."*

*"Since using rhGH treatment my muscles have strengthened and I am able to walk, kneel and rise, get in and out of the bath, do the cooking, cleaning, shop and all the usual things that one does without any trouble."*

### CURRENT LIFE

In 1997 Peter and his wife moved to Winchester, in preparation for retirement. He planned to work for another 5 years and then stop clinical activity. He established a 'stable isotope unit' run by Margot Umpleby, now Professor at Guildford, with £1 million raised by a diabetic patient's mother (The Hordern Fund). With Richard Jones he developed a patent on 'hepatoselective pharmaceutical actives' and conducted a series of metabolic studies, largely carried out by David Russell-Jones, on the effects of GH, IGF-1 and insulin in adults with and without GH deficiency. In 2001, Peter was invited to give a 'swan song' lecture at the Society BES meeting entitled 'Insulin, GH and sport'.<sup>10</sup>

On 30 September 2001 he retired and stopped all clinical work. On 27 December 2002, 3 days after a \$1 million US Anti-Doping Association award, Peter had his skiing accident and his 'new life began'.

*"The effects of rGH on body composition and metabolism in adults with GH deficiency led to a publication that has been cited over 1000 times"*

He is very philosophical about his injury, which I find inspiring given the effect it must have had on him and his family. As we chat, his computer flashes up photographs of his family and friends. He has two children from his first marriage; his son is an anaesthetist in the West Midlands and his daughter a radiologist in Brighton. Sönksen lives a very active life, and publishes original research, review articles and book chapters. He holds regular research meetings with Richard Holt and their research group at his house.

*"Sönksen's method of detecting GH abuse was used at the London 2012 Olympics and Paralympics, successfully catching two cheats missed by the previous test"*

Peter practises what he preaches. He has taken GH and testosterone replacement since his accident, and is convinced this has helped his recovery and maintains his strength. He is planning a GH-testosterone-oestrogen trial on frail elderly patients admitted with their first neck of femur fracture, and has many views on the 'somatopause'.

Sönksen's 'marker method' of detecting GH abuse has been approved by the World Anti-Doping Agency and the IOC, and was used for the first time at the London 2012 Olympics and Paralympics, successfully catching two cheats who were missed by the previous test.

As I journey home, I reflect on the last few hours. Sönksen has definitely given the best argument I have heard for ages regarding the importance of studying diabetes and endocrinology together; he was unimpressed when I told him I mainly do endocrinology these days. I think he would have done well whatever he put his mind to. If he had got ethical approval for his 'flu vaccine in the early 1970s, he would have probably followed his nose and become a successful academic haematologist. I reflect on how he has overcome his adversity and how much he has achieved in his career. More than anything, having met Peter Sönksen, I am left thinking that you can't keep a good man down.

MILES LEVY

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## CALL FOR NOMINATIONS 2015 MEDALS

The Society awards several medals annually, in recognition of outstanding contributions to endocrinology. All members are invited to make nominations. Forms can be found at [www.endocrinology.org/about/medals.html](http://www.endocrinology.org/about/medals.html). They should be returned by 31 July 2013.

The **Dale Medal** is the highest accolade bestowed by the Society, and is awarded to an individual whose studies have changed our understanding of endocrinology in a fundamental way. Previous recipients include BW O'Malley, RM Evans, KS Korach, ER Simpson, S O'Rahilly, M Thorner, AS McNeilly and S Lamberts.

The **Society Medal** is awarded to an endocrinologist working in the UK, in recognition of outstanding studies. It has previously been awarded to A Loudon, M Korbonits, IS Farooqi, GR Williams, W Arlt, A Hattersley, HOD Critchley and BR Walker.

The other medals are intended to promote links between the UK and different areas of the globe.

The **European Medal**, presented to an endocrinologist in mainland Europe, has previously been awarded to T Visser, A Spada, JJ Holst, X Bertagna, B Allolio, W Wiersinga, N Skakkebaek and AM Colao.

The **Hoffenberg International Medal** (formerly known as the Asia and Oceania Medal and the International Medal) is awarded to an endocrinologist from outside the UK, to promote international collaboration. Previous recipients include RI McLachlan, F Labrie, G Karsenty, PJ Fuller, T Yoshimura, M Kawata, K Ho and K Morohashi.

The **Transatlantic Medal** is awarded to an endocrinologist working in North America, and has previously been received by M Lazar, MJ Meaney, P Sassone-Corsi, JJ Kopchick, S Melmed, L Jameson, R Rosenfeld and B Spiegelman.

## YOUNG ENDOCRINOLOGISTS' PRIZE LECTURES 2013

Following a call for abstracts which were marked by the Nominations Committee, we are delighted to announce the winners for 2013.

The basic science prize winner is Dr Carles Gaston-Massuet (University College London Institute of Child Health) for his abstract 'Pituitary development: the answer is blowing in the Wnt'. Dr Gerard Walls (University of Oxford, OCDEM) won the clinical prize for his abstract 'Clinical and pre-clinical studies of neuroendocrine tumours (NETs) in multiple endocrine neoplasia type 1 (MEN1), and evaluation of MEN1 gene replacement therapy for MEN1-associated NETs'.

Both winners will present their work at the Society BES 2013 meeting.

## YOU & YOUR HORMONES: THANKS TO CONTRIBUTORS

We are grateful to the following, who have contributed to the Society's public information website, You & Your Hormones ([www.yourhormones.info](http://www.yourhormones.info)):

Dr S Chouliaras (Manchester)  
Ms C Duval (Manchester)  
Dr J Gardiner (London)  
Dr S González-Seña (Leeds)

Dr Z Hassan-Smith (Birmingham)  
Dr A Joshi (Sunderland)  
Mr M Khan (Liverpool)

Mr L Nardo (Manchester)  
Dr R Poole (Poole)  
Dr M Thida (Leeds)

## REDEFINED SCOPE FOR SOCIETY JOURNALS

*Journal of Endocrinology* (JOE) and *Journal of Molecular Endocrinology* (JME) are the two Society for Endocrinology journals that primarily focus on the publication of basic science.

To best support members and authors, we must offer clear choices to those who submit papers to these journals. Consequently, we are diverging the scopes of the two journals so that each has a distinct focus, while together they still cover the whole of basic endocrinology.

### PHYSIOLOGY, METABOLISM AND TRANSLATION

<http://joe.endocrinology-journals.org>

*Journal of Endocrinology* will focus on endocrine physiology and metabolism, including hormone secretion, hormone action, and biological effects. The journal will consider basic and translational studies at the organ, tissue and whole organism level. It will publish original research articles, rapid communications and reviews.



### MOLECULES, CELLS AND MECHANISMS

<http://jme.endocrinology-journals.org>

*Journal of Molecular Endocrinology's* focus will be on molecular and cellular mechanisms in endocrinology, including gene regulation, cell biology, signalling, mutations, and transgenesis. The journal will consider basic and pathophysiological studies at the molecule and cell level. It too will publish original research articles, rapid communications and reviews.



The Editorial Boards of the two journals will be combined under the Editorship of Professor Adrian Clark, St George's, University of London. This will ensure the suitability of your work is matched to the journal, increasing its visibility to the right audience.

## POSTGRADUATE ESSAY PRIZE WINNERS

Congratulations to Syed Hussain (Imperial College London), who has won the Society's £1000 prize for his postgraduate essay 'Feeling nervy about diabetes? Perhaps it's in your head'. You can read an abridged version on page 16 of this issue. Two runners-up won prizes of £125: Liliane Chamas (Oxford) for her essay 'Help from my little friends ...', and James Stillit for his essay 'It's a Man's Man's Man's World'.

## 'COMFORT IN CHANGE' FROM OUR SCIENCE COMMITTEE CORRESPONDENT

Last week I had my face painted green, wore a brown frock and declared myself to be queen of the forest. No, not the result of repeatedly putting my head too far into the fume hood, rather a cameo part in the medical school pantomime. I would like to report that 'Darling, I was marvellous!' but I think 'tremulous' would be a better description. All my carefully rehearsed intonations to deliver arch-dame campness melted under the stage light glare. What was meant to be Dame Maggie Smith in Downton came over as Grant Mitchell in arboreal drag.

Switching roles and being told what to do by student directors was initially hugely unsettling. I was surprised how uncomfortable this reversal in position made me feel. Aren't I supposed to be the person running the show, controlling and coordinating? That said, once I got over myself and realised that the whole point was to make me look ridiculous (job done there), I found my involvement to be a complete blast. The joyous energy of the production team was infectious and spilled over into the rest of my working week.

I was also buoyed by the fact that I had done something different, because I fear that normally, when times are tough and things aren't working, I have a habit of migrating to the comfort of the familiar, just to be assured I can at least do something right. But maybe an over-attachment to familiarity can be self-defeating, making uncertainty and the unknown ever more threatening.

To be clear, I do not subscribe to change for change's sake, nor do I believe that new and different equates with better. There are values and visions that should remain sacrosanct and are worth fighting for in an often vacuous, 'on-trend' world.

However, no format need be forever. Change offers fresh challenge and perspective. I am delighted to assure you that your Science Committee likes change too. This is not some ossified politburo, wielding unbridled nepotism to maintain established interests. We are a concerned body of practising research scientists trying to make sure the portfolio of activities we support are fit for purpose and fit to you. If a funding stream works and bright people with good ideas get a boost then great; if not, it's time to rethink.

If you feel there are fields or individual groups too long ignored, that require support, let us know. If you see changes in what we offer tell us what you think, good or bad. We are keen to continue to ruffle things up, even just a little, not only because it's the right thing to do, but also because it makes life so much more enjoyable.

TONY COLL

Contact  
[members@endocrinology.org](mailto:members@endocrinology.org)



## 7TH HAMMERSMITH ENDOCRINE SYMPOSIUM

The Society for Endocrinology sponsored the 7th Multidisciplinary Endocrine Symposium at Hammersmith Hospital on 7 December 2012. This annual meeting brings together trainees and consultants from all specialties who manage complex endocrine patients in multidisciplinary teams, to share best practice and discuss difficult cases. The 190 delegates included 80 patients with pituitary disease and 10 patients with multiple endocrine neoplasia (MEN), who attended the main meeting and the parallel sessions specifically designed for them.

This year's meeting had a strong thyroid emphasis. We were updated in thyroid ultrasound by Chris Harvey (Hammersmith) and in current surgical strategy in differentiated thyroid cancer by David Scott-Coombes (Cardiff). Stephen Robinson (St Mary's, London) reviewed the potential side effects of suppressive doses of thyroxine in patients with thyroid cancer, and Will Drake (St Bartholomew's, London) enlightened us with some excellent thyroid case discussions, accompanied by interactive clickers. Trainees then presented interesting thyroid cases with input from the audience. Anders Bergenfelz (Lund, Sweden) delivered the Society for Endocrinology Seminar, with a thought-provoking lecture on complications of thyroid surgery in the elderly.

The delegates viewed the excellent posters over lunch. The Society supported a prize for the best poster, which was awarded to Ian Seetho (Derby).

Jeremy Cox (St Mary's, London) began the afternoon with a review of who needs genetic testing for primary hyperparathyroidism. Following some excellent neuroendocrine tumour case-based discussions, the audience was treated to a fascinating lecture on familial pituitary tumours by Márta Korbonits (St Bartholomew's, London): did you know that up to 7% of your pituitary patients are likely to have familial disease? Fausto



Will Drake discusses difficult thyroid cases

Palazzo (Hammersmith) concluded the meeting by outlining how a retroperitoneoscopic approach can be used to access the adrenal gland in 1 min 39 secs, with patients having a rapid recovery and being discharged usually within 24 hours.

As well as providing a Sponsored Seminar Grant, the Society also supplied 50 blue T-shirts bearing the phrase 'Endocrinologists do it with hormones' in large white lettering. These proved immensely popular and disappeared within minutes!

You can enjoy all the abstracts at <http://metmed.info>. Preparations are underway for the 8th Hammersmith Endocrine Symposium on 6 December 2013.

## MEASURING SUCCESS

WRITTEN BY CHRIS GIBSON

Nurses are drawn to endocrinology via many pathways. Unlike medicine, there is no set training for the specialty in adult nursing, and yet the skills and attributes required can be diverse and challenging. Nurses often enter with little or no background in the subject and learn in post, but until now without an established framework to measure success.

This was an issue identified by the Society's Nurse Committee, which looks to support novice to expert endocrine nurses. It was also recognised that consultants need to work with highly skilled nurses, to complement the endocrine services in their area.

A working party of carefully selected experienced nurses was invited to take part in drafting competencies related to caring for endocrine patients in a nursing capacity. The nine competencies were identified by the nurses themselves, using key indicators of capability in each targeted area. They are acromegaly, Cushing's, dynamic function testing, growth hormone deficiency, hypogonadism, hypopituitarism, steroid replacement therapy, thyroid and transition.

*"It is hoped the competencies will help nurses measure their performance against a national benchmark"*

Group members discussed the skills, knowledge and aptitude required for each topic and how to demonstrate the level of expertise reached and set targets for future development. Level of ability in each instance is defined as competent, proficient or expert. In this way, nurses can set their goals in conjunction with the endocrine team, in order to benefit the local service.

Some nurses may not have the opportunity to reach the expert level in all the identified areas, due the nature of the work they do. However the document that has been drafted is meant to be fluid and allows for adaptation where necessary. It is also the first part of an ongoing process where further competencies will be added as the document is used and evaluated.

The tool can also be used by managers for appraisal and monitoring purposes, providing definitive criteria to quantify expertise. Significantly, it is hoped the competencies will help nurses to measure their own performance against a recognised national benchmark, raising the standard of care achieved for endocrine patients.

The printed text will be circulated to all hospitals with an endocrine department and a PDF will be available at [www.endocrinology.org/endocrinurse](http://www.endocrinology.org/endocrinurse).

An abstract detailing the formation of the tool has been submitted to the Society BES 2013 meeting, and a presentation on the subject is planned for the nurses' session at ECE 2013.

CHRIS GIBSON  
ON BEHALF OF THE WORKING PARTY

## ANOTHER NEW YEAR ALREADY!

WRITTEN BY NIKKI KIEFFER

As you can see the exciting news is that all the adult endocrine nurse competencies have now been completed and we are in the final stages of preparing the document for publication. We aim to have this sorted by the Society BES meeting in March - hope to see you there. I would like once again to thank all those who have been involved in the development of this document for all their hard work.

The committee continue to work on your behalf and will be meeting soon to finalise the programme for Endocrine Nurse Update in September, begin working on the nurses' sessions at next year's Society BES meeting, and any other business. This year's Endocrine Nurse Update will be in Stratford-upon-Avon on 16-17 September 2013, so please put the date in your diary.

We welcome three new members to the committee this month, Julie Andrew (Leeds), Louise Breen (Leeds), and Sofia Llahana (London). I look forward to working with them all.

Finally, the nurses' sessions at this year's Society BES are on Wednesday 20 March 2013. If you intend to attend the whole of the meeting don't forget to register in good time to take advantage of the reduced rate for early registration.

See you there.

NIKKI KIEFFER



## THERE'S MORE TO AMEND...

WRITTEN BY JO GREY

The Association for Multiple Endocrine Neoplasia Disorders (AMEND) was 10 years old in 2012, and now has a membership of over 500.

What struck me when I gave presentations recently at the Society for Endocrinology Endocrine Nurse Update and the British Association of Endocrine and Thyroid Surgeons Annual Meeting was how little was known about what AMEND actually does. So, for the benefit of those of you who must just be too shy to come and visit our exhibition stand at the Society BES and other meetings, here is a read-at-your-leisure summary of our activities:

- AMEND is well-organised with a committed team of volunteers (patients and expert medical advisors). Our strategy considers and addresses the needs of our beneficiaries and we are transparent about our work. Beware groups who do not work in this way; they do exist and we have picked up the pieces of the patients who have been there.

- AMEND is currently supporting two patient members as they develop affiliated non-profit patient groups in the USA and New Zealand.

- AMEND's main aims are to educate, support and befriend families affected by multiple endocrine neoplasia (MEN) and associated endocrine tumours, and to promote research into the conditions. Advocacy has become an additional recent focus.

### EDUCATION

Our free educational resources are highly valued and include our website, which was launched in 2012 and houses our MEN patient experience films, forum, information library and much more.

We also produce hospital leaflets, and a range of patient information titles: *MEN1*, *MEN2a*, *MEN2b*, *FMTC* (familial medullary thyroid carcinoma), *MTC*, *Phaeochromocytomas and paragangliomas*, *Talking to children and young people about MEN*, *Whipple's procedure*, and *FIPA* (familial isolated pituitary adenoma).

We have just begun a new 2-year project to provide educational resources for children and teenagers: Project Superhero! Funded by the Big Lottery Fund, it will produce comic books and website animations on *MEN1* and *MEN2* to help affected families talk about these genetic conditions with their children and to help engage youngsters more effectively in their healthcare.

### SUPPORT AND FRIENDSHIP

The importance of support services to increase patients' emotional well-being should not be underestimated. Our free services are available for MEN patients, patients with associated sporadic tumours, those with SDHx (succinate dehydrogenase-related) syndromes and others on request.

AMEND's Annual Patient Information Day held in May each year and our periodic local area meetings are popular with patient members, who value the opportunity to talk with others and to quiz our brave visiting medical experts at the Q&A sessions!

All of our patient members are contacted every 6 months for a 'check-up' by one of our trained 'Telebuddies', providing a unique opportunity for them to off-load, when perhaps they hadn't realised they needed to.

Our counselling helpline provides fast access to help for patients and their families when they reach crisis point.

### ADVOCACY

AMEND provides a patient voice in a growing number of arenas: the European Medicines Agency, the National Cancer Intelligence Network Thyroid Cancer Working Group, the National Institute for Health Research, the British Thyroid Association, and within the patient-led setting of the World NET Cancer Day Alliance.

### RESEARCH

AMEND funds an annual Young Investigator Award in association with the Society for Endocrinology at the Society BES meeting.

AMEND's own Research Registry is a simple initiative to connect researchers with patients. Patients can opt to register when applying for free AMEND membership. Over 250 already have, and the Registry was used successfully four times in 2011, including by Birmingham University and the MD Anderson Cancer Center in the USA.

2012 saw the first ever AMEND Research Award: a £5050 grant to the University College London Hospitals for a study into prophylactic thyroidectomy in *MEN2* children in the UK.

To add to our coffers, in autumn 2012, nine members of AMEND, nicknamed the 'Maniac Endocrine Nomads', (pictured) successfully braved searing heat, sandstorms, rain and D&V to trek 120km through the Sahara Desert, raising over £14000 in the process.

For more information on how AMEND can help you and your patients, please visit us at [www.amend.org.uk](http://www.amend.org.uk), or come to our stand at the Society BES 2013 meeting in Harrogate - I dare you!

JO GREY  
CEO, AMEND





## THYROID VIDEO FOR CHILDREN

Few resources have been available to support children with thyroid disorders and their families, and so the British Thyroid Foundation (BTF) is delighted to have funded an animated film for children on this subject.

The 6-minute film is aimed at children aged 6–12 and is intended for them to watch on their own or with their families and carers. Entitled 'Your thyroid broke ... but we can fix it', the film deals with hypo- and hyperthyroidism. It was launched at the British Society for Paediatric Endocrinology and Diabetes meeting in Leeds in November.

If you would like to receive copies for use in clinics or to be handed out to patients then please contact [children@btf-thyroid.org](mailto:children@btf-thyroid.org). The animation can also be seen on the BTF website: <http://bit.ly/QRNuh5>.

The BTF is grateful to the Society for Endocrinology and Bettys & Taylors of Harrogate, who donated grants towards the cost of the film. The BTF is a patient support organisation that provides information and advice for people with thyroid disorders. You can read more about its work at [www.btf-thyroid.org](http://www.btf-thyroid.org).



The Society for Endocrinology helped to fund this project via a Patient Support Grant made to the BTF in 2012. Full details of all grants awarded can be found on our grants web page ([www.endocrinology.org/grants](http://www.endocrinology.org/grants)). Another round of awards will open soon – so watch this space.

## OBESITY: RCP CALLS FOR COORDINATED ACTION

WRITTEN BY JOHN WASS



The medical problems of obesity in the UK are the focus of a recent report from the Royal College of Physicians (RCP). This report, 'Action on obesity: comprehensive care for all,' has been compiled over the last few months by a group led by myself and Nick Finer ([www.rcplondon.ac.uk/resources/action-obesity-comprehensive-care-all](http://www.rcplondon.ac.uk/resources/action-obesity-comprehensive-care-all)).

We performed a major survey of multidisciplinary obesity services up and down the country, with which many of you kindly helped. This identified major gaps, indicating that only about 37% of the population are served by multidisciplinary obesity services to whom they can be referred for active treatment. Clearly these voids need filling, and the report outlines the steps necessary for this.

*“Only about 37% of the population are served by multidisciplinary obesity services to whom they can be referred for active treatment”*

In parallel with this activity, a group chaired by Julian Barth is setting out the requirements under the NHS Commissioning Board (the group of services which will be commissioned nationally as opposed to locally), regarding severe complex obesity. We narrowly avoided this being called bariatric surgery! A very sensible commissioner is also involved. The aim is to develop services, and one of our concerns is that the hubs and spokes should expand, and that there are not enough of either at the current time.

Returning to some other issues in the report, we highlight the problem that health care workers generally have a high prevalence of obesity, but that these people are poorly catered for in their employment. By interacting with occupational health physicians and setting up a template for Trusts which suggests healthy eating policies, exercise facilities and other aspects within the employment environment, we aim to encourage better diets and the maintenance of healthy weights.

We want to see a Patient Charter. We are keen to see the creation of a more formal group of bariatric physicians. Shahrar Taheri is leading on this initiative, and we very much hope it might become part of the Society for Endocrinology. We want to see QOFs for adults and children which will encourage GPs to refer relevant patients to weight management services that have been shown to be effective, as well as to other services as they are set up.

The report also suggests the formation of a group at the RCP to ensure that these suggestions come to fruition. Many reports gather dust on shelves, and we are determined that these issues are met with swift action. The first meeting will take place at the RCP in London in February.

Lastly, the report suggests active involvement of central Government. The complex problem of obesity has not been overcome by any nation on the planet, and part of its complexity is due to the need for action by a number of dis-coordinated Government Departments. As well as the Department of Health, these include the Treasury, and the Departments of Education, Sport, Agriculture, Work and Pensions, and others. In the report, we suggest appointing an individual, such as a crossbencher in the House of Lords, who could coordinate activity between Departments. Unfortunately, the Cabinet Committee on Public Health, through which the group might have effectively reported, has recently been disbanded, but we remain focused on identifying an appropriate alternative.

## ADRENAL CRISIS: A PROACTIVE APPROACH

Some time ago, a GP friend in Oxfordshire talked to me about difficulties he had had obtaining steroid treatment for his mother-in-law. She is a known Addisonian patient. Katherine White of the Addison's Disease Self Help Group has also pointed out this problem when patients with known Addison's disease go into hospital in crisis. Furthermore, the Royal College of Physicians (RCP) received a letter from a coroner saying that a patient had died after surgery for craniopharyngioma without adequate steroid cover and unsupervised by an endocrinologist.

*“14% of Addisonian patients die in crisis”*

We decided to take a proactive approach to this problem and, together with Wiebke Arlt, wrote a leader article for the *BMJ* (2012 345 e6333). This highlighted the difficulty that some patients have getting steroids and the resulting potential fatality (14% of Addisonian patients die in crisis). We also emphasised the guidelines which have been published (by the Society for Endocrinology, the Addison's Disease Self Help Group and the Pituitary Foundation). These cover what to do in crisis and how best to cover operative intervention in patients who either have primary or secondary adrenal failure.

Of course, others are at risk, and any patient who is on 5mg prednisolone or more for longer than a month may be adrenally

suppressed. It is known that inhaled steroids and widespread skin application of steroid creams may also suppress the adrenal gland. The BNF needs updating in this respect too, and we have raised the issue with Neil Gittos who is the BNF's endocrine guru. Patients with congenital adrenal hyperplasia, albeit a rarer group, sometimes have adrenal crisis.

We have drawn the attention of the Addison's Disease Self Help Group, the Pituitary Foundation and the congenital adrenal hyperplasia charities to the leader article, so that people can take the document into casualty with them when they are admitted and point out the urgency of steroid replacement therapy.

To further highlight the problem, we have written to the Royal College of Surgeons, and are writing a leader for *Journal of Emergency Medicine*. We have ensured that it is on the General Medical Curriculum at the RCP. I am meeting the lead on education at the Royal College of Nursing, so that this is highlighted in their curricula. By contacting the head of the ambulance paramedics, we are trying to make sure that all ambulances are enabled to give hydrocortisone to patients with known adrenal insufficiency in an emergency.

Rowan Hillson, the Diabetes and Endocrine Tsar, has been contacted, and our aim is to make it rather like insulin omission – a 'never-event' – under the aegis of the Department of Health.

*If there is anything else you think we can do please let us know. This is obviously an important avoidable endocrine fatality.*

JOHN WASS

## RCP TRAVELLING BURSARIES

Trainees in endocrinology and diabetes mellitus may apply for these bursaries, which will be awarded to those wishing to attend any conference organised by the Royal College of Physicians on or including the topics of endocrinology/diabetes mellitus. The bursaries may cover conference registration fees, standard/economy class travel and accommodation if necessary. Up to five awards will be made throughout the year, funds permitting.

Applications should be made in writing, enclosing a CV and giving full details of the expected costs for the event to be attended. They should be submitted to the academic vice-president (Email: [trustfunds@rcplondon.ac.uk](mailto:trustfunds@rcplondon.ac.uk); Tel: 020 3075 1564; Fax: 020 7224 0719).

## CLINICAL ENDOCRINOLOGY TRUST FUNDING FOR QUALITY IMPROVEMENT PROJECTS



The Clinical Endocrinology Trust is a charity which derives its income from a profit-share of the Society for Endocrinology's official clinical journal, *Clinical Endocrinology*. It has long supported endocrine audit projects within the UK. Recent examples include the UK Acromegaly Database, the CaHASE audit of adults with congenital adrenal hyperplasia, the national audit of cabergoline and valvulopathy, and a British Thyroid Association study of teenage iodine status across the UK.

The Trustees now invite further applications from societies or endocrine centres. Preference will be given to projects involving multicentre collaborations. We are particularly interested in receiving applications related to areas of endocrinology the Trust has not supported previously. A sum of £50 000 is available during 2013–2014 for a number of projects judged by the Trustees to be worthy of support: their decision will be final. Projects must commence within 6 months of an award being made.

The closing date for applications is 28 June 2013. Forms are available from [judith.toon@manchester.ac.uk](mailto:judith.toon@manchester.ac.uk) and should be returned to Professor Julian Davis (CET Secretary) at [julian.davis@manchester.ac.uk](mailto:julian.davis@manchester.ac.uk). The Clinical Endocrinology Trust looks forward to hearing from you!

## CONGRATULATIONS...

Society for Endocrinology member Peter Trainer has been nominated for the position of President-Elect of The Endocrine Society, alongside Richard Santen (University of Virginia).

Voting for the position is closed to The Endocrine Society members and ends on 3rd March 2013.

We will bring you the result of the vote when announced.





## FEELING NERVY ABOUT DIABETES? PERHAPS IT'S IN YOUR HEAD

Speaking as one of the 347 million diabetics in the world today, I think we owe Banting, Best and their dog Marjorie a lot. If it was not for them and what followed perhaps we would still be considering lettuce leaves and water to keep people like me alive. But nine decades and several Nobel prizes later, it seems that we are still learning how the body controls glucose with such precision, and more importantly why it goes wrong.

WRITTEN BY SYED HUSSAIN

Our school biology teacher taught us that the regulation and control of blood glucose was all about a negative feedback circuit, with the clever pancreas responding to fluctuations in glucose by releasing insulin or glucagon accordingly to keep glucose levels tightly controlled, much like a radiator thermostat. Those painful hours I spent as a young teenager learning this important concept proved fruitful, as up till now all my lecturers and textbooks have sung from the same hymn sheet. But whilst this negative feedback by the pancreas holds true, it cannot explain how the body is able to control glucose levels depending on its needs, and anticipate what to do before glucose levels change. There must be something more...

It turns out that the brain plays an important role in controlling the body's glucose levels. And why wouldn't it? Glucose is the main energy source for the body. The brain relies almost entirely on glucose for energy and needs this energy to work properly. The brain 'knows' what you are up to - whether you are eating, fighting, fleeing, actively reproducing or lying on the couch reading *The Endocrinologist*. It can integrate all this information and respond appropriately to control other important systems and hormones such as breathing, circulation, temperature, thirst, hunger, reproduction, stress and metabolic rate. So why not glucose?

In fact, the first hint of the brain's ability to control glucose was illustrated by the French physiologist Claude Bernard in 1855. He demonstrated high glucose in rabbits after puncturing a small part of their brain, and concluded that the CNS regulates glucose levels. After the discovery of insulin in 1921, this effect became largely forgotten as much of the focus shifted to the pancreas and biochemistry of insulin. However, recent work has rekindled interest in this long forgotten effect of the brain's ability to control glucose.

### HOW DOES YOUR BRAIN SEE SUGAR?

The brain has specialised cells that are capable of detecting and responding to glucose.<sup>1</sup> These glucose-sensitive cells are located mainly in the hypothalamus, which is the key homeostatic, endocrine and autonomic regulator of the body. The mechanisms by which these brain cells sense glucose are similar to those seen in insulin-secreting cells of the pancreas. The brain is not just capable of sensing glucose - it is a lot smarter than that. As a result of hormone receptors, biochemical nutrient-sensing mechanisms and leaky capillaries near the hypothalamus, the brain can sense alterations in hormones related to digestion and energy homeostasis such as insulin, glucagon-like peptide-1 and leptin, as well as nutrients such as fatty acids and amino acids.<sup>1</sup> The brain is also influenced by a variety of other physical and

psychological stimuli such as temperature, smell, taste, anxiety, reward and stress. How and where all this information is integrated is not completely understood; however, the hypothalamus and brainstem are thought to be key players.

### HOW DOES YOUR BRAIN CONTROL SUGAR?

Earlier work demonstrated that lesions and altered delivery of glucose to specific parts of the hypothalamus can change insulin, glucagon and glucose levels.<sup>2</sup> The last decade has seen a marked improvement in our ability to selectively alter precise brain cells and accurately phenotype rodents, which has helped address these questions more directly. Recent work demonstrates that alterations in hormones and nutrient sensing by the brain in rodents leads to marked changes in glucose control. Evidence suggests that distinct regions of the brain have roles in controlling blood glucose in response to changes in glucose, insulin and fatty acids.<sup>2,3,4</sup> These discrete brain nuclei regulate glucose output from the liver, insulin resistance, counter-regulatory responses to hypoglycaemia, glucose-stimulated insulin and glucagon release from the pancreas.

### HOW DOES YOUR BRAIN TELL THE PANCREAS AND LIVER WHAT TO DO?

Observations in the late 20th century suggested blood glucose levels and hormones, such as insulin and glucagon, are influenced by the autonomic nervous system (ANS).<sup>5</sup> Nerves from the ANS innervate almost every organ in the body including the cells and blood vessels of the pancreas and liver. The 'wandering' vagal nerve is necessary for the brain to influence blood glucose. The ANS can influence insulin release, glucagon release, liver glucose output and even the size and number of insulin-producing cells in the pancreas.<sup>2</sup> Interestingly, defects in all these aspects are found in the major form of diabetes. Exactly how these nerve fibres regulate hormone release is still being slowly unravelled.<sup>6</sup>

### WHAT RELEVANCE IS THIS TO NORMAL PHYSIOLOGY?

Perhaps we can't rewrite the textbooks just yet, as the pancreas is undoubtedly vital to controlling blood glucose, but the involvement of a brain-endocrine pancreas axis and a brain-liver axis is becoming more apparent. These brain axes explain how glucose levels are finely tuned to metabolic needs and can vary in anticipation of certain situations like eating, exercise and stress. The last time you scoffed a piece of cake, your body churned out insulin even before your gut had a chance to digest and absorb glucose. The pancreas did not see this glucose coming but was told to release insulin by a cephalic insulin response arising in the

hypothalamus via the vagus nerve.<sup>7</sup> The last time you ran to catch the bus, amongst a number of other things, your brain ensured that blood glucose levels stayed up by telling your liver to release more glucose from its stores, telling your pancreas not to increase insulin release and keep releasing glucagon. It does this and more all the time, to ensure that glucose levels meet the needs of your body.

### IMPLICATIONS AND FUTURE

Despite new treatments and improved ways to deliver insulin, diabetic patients still develop serious complications due to their inability to restore natural glucose, insulin and glucagon patterns. For example, some diabetic patients on insulin develop defective responses to counteract low blood sugar, leaving them more exposed to the serious consequences of disabling hypoglycaemia. Changes in the brain's ability to sense glucose may cause this defect.<sup>8</sup> Understanding how the brain regulates glucose may allow us to develop new and better treatments for diabetes. It also raises some interesting questions. Is the rise in diabetes the consequence of a selfish brain promoting glucose levels to cover its own high energy requirements? Is this similar to a selfish brain promoting hunger to cause obesity? Indeed, the parallel epidemics of obesity and diabetes may have a common origin in hypothalamic dysfunction. In rodents, high fat diet consumption leads to defective hypothalamic glucose-sensing and hypothalamic inflammation, both of which lead to insulin resistance and glucose intolerance.<sup>9,10</sup> So is the major form of diabetes, in fact, a disease of the brain?

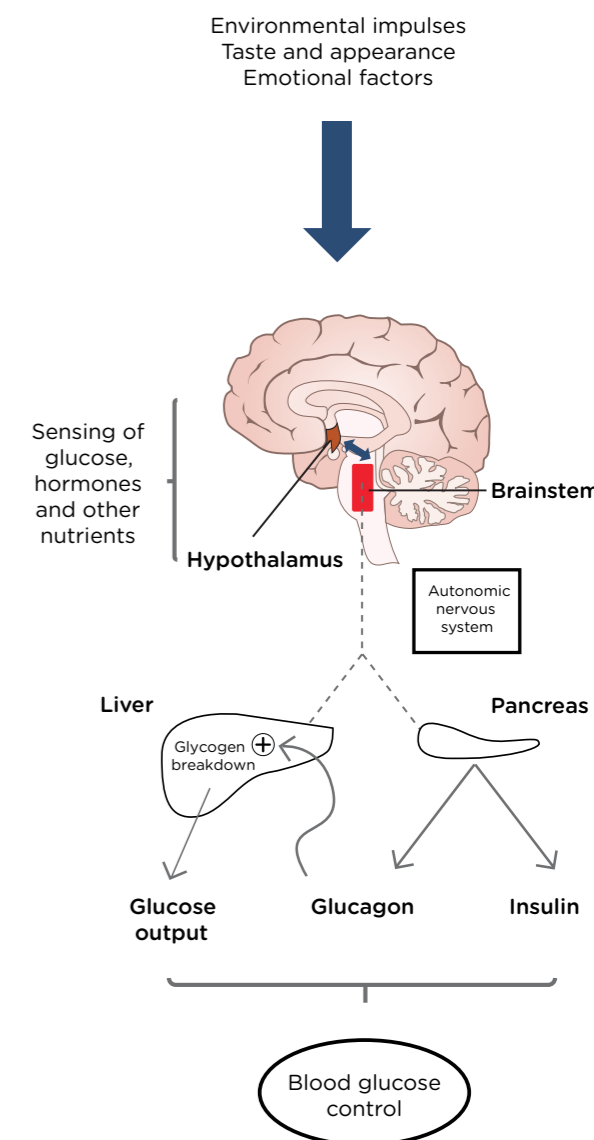
Much remains to be learnt, but it seems that the brain may be ready to regain its lost reputation as a regulator of glucose homeostasis. So feeling nervy about diabetes might be a good thing. It may allow us to use our heads to treat this growing problem.

SYED HUSSAIN

Syed Hussain is the winner of the Society for Endocrinology Post-Graduate Prize Essay. We are pleased to publish a slightly abridged version of his essay here (to read the full version, see [www.endocrinology.org](http://www.endocrinology.org)).

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The hypothalamus senses signals and influences the brainstem, where the autonomic nervous system originates. This controls liver glucose output, glucagon and insulin release.

## MACKENZIE ON ALDOSTERONE

WRITTEN BY SCOTT MACKENZIE



Being invited to contribute to this new series on 'favourite' hormones made me address several questions for the first time. I have worked on aldosterone for many years, but is it really my favourite hormone? Do I actually harbour secret yearnings to dabble in, say, vasopressin or insulin? And what kind of weirdo has a favourite hormone anyway?

Well, after some reflection, I came to the inescapable conclusion that I am precisely the kind of weirdo who has a favourite hormone and that, for better or worse, my favourite hormone is aldosterone.

Although some of my affinity for aldosterone is undoubtedly the result of having worked on it for so long – a kind of twisted, scientific Stockholm syndrome – I also realise that I wouldn't have devoted so much of my time to it if I did not believe it to be rather fascinating and extremely important.

### BODYBUILDING, SEX CHANGES AND STRANGE RASHES

This importance is often overlooked. In the public perception, aldosterone does not enjoy the same recognition as other steroid hormones. Indeed, when I let slip to a non-endocrinologist that I work on steroids, I am generally met either with a glazed expression and a rapid change of subject, or else by a sudden spark of recognition followed by a wide-ranging monologue touching on bodybuilding, sex changes and a strange rash they once had. Aldosterone and its role in blood pressure regulation never get a look in.

*“All that was left for me was to tie up a few loose ends before retiring early to a tropical paradise”*

While this reaction is doubtless the result, in part, of my poor public engagement skills, it also stems from the fact that around 20 years ago we thought we had aldosterone pegged as a somewhat limited molecule, in terms of its function and impact. The skilful pioneers in this field had already demonstrated that aldosterone, produced by the adrenal cortex, regulates blood pressure by stimulating renal sodium retention, thereby increasing intravascular volume. This it achieves by binding the mineralocorticoid receptor (MR), which influences gene transcription through direct interactions with DNA.

This view was pretty much the consensus when I started my own research career in the mid-90s, and it seemed all that was left for me was to tie up a few loose ends before retiring early to a tropical paradise. Scientific reality quickly intervened.

### TANTALISING HINTS

New, sensitive molecular techniques revealed complexities in the production and action of aldosterone that, while not contradicting the existing model, showed it to be incomplete. Much of my early work arose from tantalising hints that small amounts of aldosterone might be produced outside the adrenal cortex, in brain, adipose and cardiovascular tissue. While evidence was assembled to support this phenomenon in rodents, examination of human tissue has proved negative. Until rats are able to fund their own research, I fear the story of extra-adrenal aldosterone production may end there.

On the other hand, research into the role of MRs present in those same tissues – even if their only source of activation is circulating aldosterone – has proved more fruitful. Activated MRs in the central nervous system affect blood pressure, while those in the vasculature induce vasoconstriction.

Aldosterone has another little trick up its sleeve: it can act very quickly, inducing effects in a manner too rapid to be explained by the standard genomic model, which requires gene transcription and translation of new protein. This discovery led to a long and, as yet, fruitless search for a non-genomic aldosterone receptor. The popular view is now that most of the rapid effects are mediated by MRs through some still unknown mechanism.

These additional quirks and eccentricities of aldosterone might have remained of interest to a limited few, had it not been for its emergence as a key cardiovascular hormone. While excess aldosterone was known to result in hypertension, it was thought to occur only in <1% of patients with essential hypertension. This turned out to be a massive underestimate: up to 15% of such patients are now calculated to have high amounts of aldosterone relative to their renin or electrolyte levels. Although their aldosterone is inappropriately high, these patients' levels are often still within the generally accepted normal range, and this undoubtedly contributed to the delay in this discovery.

*“When I let slip to a non-endocrinologist that I work on steroids, I am met by a sudden spark of recognition followed by a wide-ranging monologue touching on bodybuilding, sex changes and a strange rash they once had”*

Aldosterone's physiological consequences, it appears, have also been played down. Through the RALES and EPHESUS trials, blockage of aldosterone access to the MR was shown to have large and significant impacts on cardiovascular mortality and morbidity. But to what extent does this benefit stem from reduction in blood pressure, or from other effects such as protection of cardiac MRs, whose activation results in cardiac hypertrophy and fibrosis?

### RECENT WORK

Our own work has focused on the CYP11B2 gene that encodes aldosterone synthase. This enzyme catalyses the final stage in a biosynthetic sequence that extends back to cholesterol, and ends here with the conversion of deoxycorticosterone to aldosterone. The gene has various structural features that make it difficult to analyse accurately, and this may be why large genome-wide association studies have not flagged CYP11B2 as being a significant factor in hypertension. However, our recent work demonstrates that common variants in the CYP11B2 gene sequence are associated not only with blood pressure levels in large populations, but also with significantly altered levels of CYP11B2 expression.

Much of our work has investigated the transcriptional regulation of this gene but, again, systems emerging in recent years have only served to complicate the picture. For example, we recently showed microRNAs to have significant influence over CYP11B2 expression at the post-transcriptional level.

The importance of aldosterone synthase in determining an individual's aldosterone levels is reflected in recent attempts by various pharmaceutical companies to develop drugs that inhibit its action. Prevention of aldosterone production may overcome the shortcomings and side effects of existing drugs, which merely block MR activation, but specific inhibition is difficult.

So, there you have it: aldosterone still presents a great number of challenges, many of which have only become apparent in the last 20 years. Their successful resolution could greatly reduce the burden of cardiovascular disease in a significant proportion of the population. Only then will I be able to focus on a far more difficult and intractable problem: it turns out tropical paradises are really quite expensive...

SCOTT MACKENZIE

Scott MacKenzie graduated with a PhD from the University of Glasgow in 2000 and is currently a Lecturer in its College of Medical, Veterinary and Life Sciences. He has been the recipient of a Hypertension Trust Research Fellowship and a Research Councils UK Academic Fellowship, and has served on the Science Committee of the Society for Endocrinology.

## CLINICAL RESEARCH NETWORKS: MAKING A DIFFERENCE TO UK ENDOCRINE RESEARCH



WRITTEN BY TARA KEARNEY & JOHN WILDING

Endocrinology has always been considered an academic specialty, and UK researchers have contributed enormously to the understanding and subsequent treatment of many endocrine conditions. Metabolic and endocrine research is often hampered not only by the rarity and complexity of such conditions, but also by limited funds, particularly a lack of commercial support. Emphasis is increasingly placed on translational and patient-centred research and financial constraints have inevitably directed funds to those areas of research that provide value for money and a direct link to improving patient care.

### COMPREHENSIVE RESEARCH NETWORKS

Major changes have recently altered the way in which UK research is organised and funded. In 2006, the National Institute of Healthcare Research (NIHR) established a Clinical Research Network (CRN), to provide a well-funded infrastructure within the NHS to facilitate the conduct of clinical trials. The aim was to double the numbers of people participating in quality research projects within 5 years.

National collaboration was required, and so specialty-specific, geographically defined networks were developed, supported by enhanced leadership, improved management and expanded local infrastructure to support the CRN remit. The structure consists of:

- Six 'Topic' Research Networks (covering cancer, dementia and neurodegenerative diseases, diabetes, medicines for children, mental health and stroke)
- A Primary Care Research Network to support research in this part of the health service
- A Comprehensive Clinical Research Network (CCRN) which covers all other disease areas.

### THE CCRN AND SPECIALTY GROUPS

The CCRN comprises 25 Comprehensive Local Research Networks (CLRNs) which cover the whole of England by region. Each of Northern Ireland, Scotland and Wales also has its own countrywide network. Nearly all of these networks have chosen to support metabolism and endocrinology, providing a nationwide network as a platform for collaboration.

Each geographic Specialty Group has a dedicated clinical lead and management team. These networks provide a national coordinating role, linking networks within and amongst disciplines to access skilled research support staff and patient populations, and to ensure structured, successful research, delivered to target and on time.

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**THE SPECIALTY GROUP:**

- Provides help for studies to get onto the portfolio
- Supports or provides the infrastructure to deliver the studies thereafter
- Monitors the adequacy of support provided for studies
- Encourages patient and public involvement in research
- Provides opportunities for researchers to contribute to studies conducted by other researchers or to access a wider patient population
- Works with the life sciences industry to promote research development
- Raises the profile of metabolic and endocrine research.

**NATIONAL PORTFOLIO**

The National Portfolio is a comprehensive list of academic and commercial high quality studies that benefit from the infrastructure provided by the CRN. The Metabolic and Endocrine Specialty Group's Portfolio includes studies on the adrenal, pituitary, thyroid, PCOS, nutrition, obesity, lipids, reproductive endocrinology, genetics, inborn errors of metabolism, bone disease and endocrine imaging.

Investigators wishing to include studies in this portfolio will find further information regarding eligibility and procedures on the CRN website ([www.crnc.nihr.ac.uk](http://www.crnc.nihr.ac.uk)). The site also has details of your local specialty CLRN lead, who will be able to advise you if you are uncertain what to do. Once your study has been approved and adopted by the Portfolio, you will benefit from CRN support. Your recruitment data should be regularly uploaded into the Portfolio to provide the current status.

You can also search the Portfolio database to see what research is being undertaken and whether other centres can take part in the studies. This is particularly beneficial in studies involving rare conditions, as is often the case in endocrinology, where many centres may need to be involved in order to achieve adequate participant numbers.

**CRN SUPPORT**

The CRN does not provide the funds to undertake research, but it does help with providing the 'infrastructure' to enable research. Examples of this include:

- Funding research support posts in the NHS, for example research nurses and clerks to assist in the day-to-day running of studies
- Part-funding of clinical research fellows to help run Portfolio studies
- Training, educational support and development of the research force
- Running the coordinated system for obtaining NHS permission (CSP), an online system enabling researchers to seek approval to undertake a study in the NHS (including ethical approval and also from individual research and development departments)
- Practical help in improving patient access, running of studies and recruiting to time and target
- Liaison with the life sciences industry to promote commercial research in the UK

Your local research and development office will be able to help you to access CRN support and can direct you to your local CLRN lead to discuss what support is appropriate. For those applying for research funds, early involvement of research and development and the CLRN is recommended.

**SUPPORTING THE LIFE SCIENCES INDUSTRY**

One of the top priorities for the CRN is liaison with the life sciences industry to deliver leading-edge research within the NHS. In recent years, clinical research was often diverted to other countries, where studies could be undertaken more quickly and often more cheaply.

The CRN is committed to ensuring that commercial clinical research flourishes in the UK. To facilitate this, the CRN has fostered strong links with our healthcare partners, appointing industry managers to nurture and develop the relationship and provide a wide range of tools and services to ensure that performance of commercial studies in the UK is exemplary.

It is essential that researchers in the UK promote their expertise and capabilities. A simple template is available for researchers to describe their talents, which can then be made available to our life science industry partners via the CRN website. We encourage all interested parties to contact [Tracey.Crofts@rlbuht.nhs.uk](mailto:Tracey.Crofts@rlbuht.nhs.uk) for a copy of the template.

**HOW SUCCESSFUL ARE SPECIALTY GROUPS?**

A recent review concluded that, overall, Specialty Groups make a major contribution to achieving the CRN's high level objectives. The review comments that 'Specialty Groups have continued to make a significant impact on delivering to time and target, engage research communities and raise awareness of what the NIHR CRN and Specialty Groups have to offer, and develop productive relationships with other stakeholders ...'

The Metabolic and Endocrine Portfolio currently has over 50 active studies, and recruited over 5000 patients to these studies during 2011–2012. Whilst this is a clear marker of success there is still much work to be done.

The goal of medical research is to improve treatment for patients, and we are beginning to work with patient groups to provide information about trials that are relevant to them, in order to improve recruitment. We continue to work closely with the Society for Endocrinology and funding bodies such as the NIHR to prioritise metabolic and endocrine research. We have successfully begun dialogue with industry, and aim to bring more commercial studies into the Portfolio.

When you are next working on a grant proposal, remember to consider how the network can support your research, or, if your existing study is struggling to recruit, whether the network can help by bringing more sites on board.

The CRN is still fairly new and processes are continuously being reviewed and refined to make it work better for researchers to the benefit of patients; we are confident the CRN will flourish as awareness and understanding of its role widens.

**TARA KEARNEY AND JOHN WILDING**  
DEPUTY CHAIR AND CHAIR RESPECTIVELY,  
METABOLIC AND ENDOCRINE GROUP OF CLRN  
[www.crnc.nihr.ac.uk](http://www.crnc.nihr.ac.uk)



**EVERYTHING YOU NEED TO KNOW ABOUT...**

**NEXT GENERATION SEQUENCING**

WRITTEN BY JASON S CARROLL

Not too long ago, people would study specific genes in pathways of interest, revealing, sometimes very slowly, an insight into their disease of interest.

In hormone-dependent cancers, this sometimes meant that an individual researcher could spend a significant part of their career studying a single protein in a single pathway, or the same promoter of an interesting target gene. For people in our field, the scale of the questions changed quickly and dramatically, almost entirely because of technological advances in sequencing.



Traditionally, sequencing involved analysis of individual pieces of DNA, one at a time. Using this approach, the first human genome sequence took many years and cost billions of dollars, yet it revealed the first full picture of our genetic make-up. Then came changes in sequencing technologies, with newer approaches, termed next generation sequencing (NGS), changing the way and the scale in which we sequence DNA.

NGS involves analysis of large numbers of individual small fragments of DNA in parallel. The pace at which NGS is evolving is incredible. One of the most popular platforms is Illumina, with each experiment producing 200 million reads (each 36 base pairs in length). This provides the opportunity to dig deeper than ever before and can be used for many applications.

**DEEP SEQUENCING FOR COMMON MUTATIONS**

One of the major benefits of NGS is the ability to find DNA mutations that contribute to a disease. By deep sequencing and comparing different samples from patients with the same disease, we can gain insight into commonly mutated genes, and ultimately expressed proteins that may be contributing to changes in disease progression or drug response.

For the hormone-dependent cancers, it turns out that it is far more complex than we probably wanted to know. Many mutations occur in regions of the genome previously considered 'junk DNA' which we now know are important regulatory regions, but we still don't completely understand the relationship between these regulatory regions and their target genes. In addition, there are many mutated genes throughout which a myriad of different mutations are scattered. The logical explanation is that since specific genes are commonly mutated, these must be contributing to the development and progression of the disease. But who is going to validate these? Currently it seems much more exciting to do genome-wide this and genome-wide that, rather than focused functional experiments.

**CHROMATIN IMMUNOPRECIPITATION**

NGS can also be used to study transcription factor biology and the role of chromatin (DNA and its associated histone proteins) in our disease models. Using chromatin immunoprecipitation (ChIP) we have been able to purify a protein of interest and assess the DNA that is bound by this factor. ChIP allows us to identify regulatory events (the switches) that the protein uses to control gene expression. By coupling ChIP with NGS, we can identify all the binding events of a factor under a specific experimental condition.

We have used this approach (termed ChIP-sequencing, or ChIP-seq) to study oestrogen receptor (ER) and androgen receptor (AR) binding events in breast and prostate cancer cells respectively. By purifying the protein of interest (such as ER) and using NGS to sift through all the associated DNA, we can identify the genomic contact points across the entire 3 billion nucleotides of the genome in one go. Against all odds, this actually works, and it turns out to be quite informative. Through analysing many thousands of binding sites in an unbiased manner, instead of a handful of favourites, it allows us to discover patterns in protein-DNA binding that can reveal mechanistic insights that we previously would have missed (see illustration).

We now know that ER (and AR) interact with regions in the middle of nowhere, that it uses additional proteins for this process, and that, through a complicated process, these regions then make loops to the promoters of target genes to switch specific genes on and off.

NGS has also revealed additional levels of regulation. Again using ChIP-seq, we can find the global maps of histone modifications (specific patterns of chemical modification added to the tails of histone proteins that the DNA wraps around), which reveal important levels of gene regulation governed

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## EVERYTHING YOU NEED TO KNOW ABOUT... NEXT GENERATION SEQUENCING

CONTINUED FROM PAGE 21

by these histone marks. Furthermore, by coupling NGS with chromatin loop assays, we can find all the loops that occur between the different regions of the genome, sometimes telling us which ER-DNA region goes with which target gene.

### AND THE ENORMITY OF THE UNKNOWN

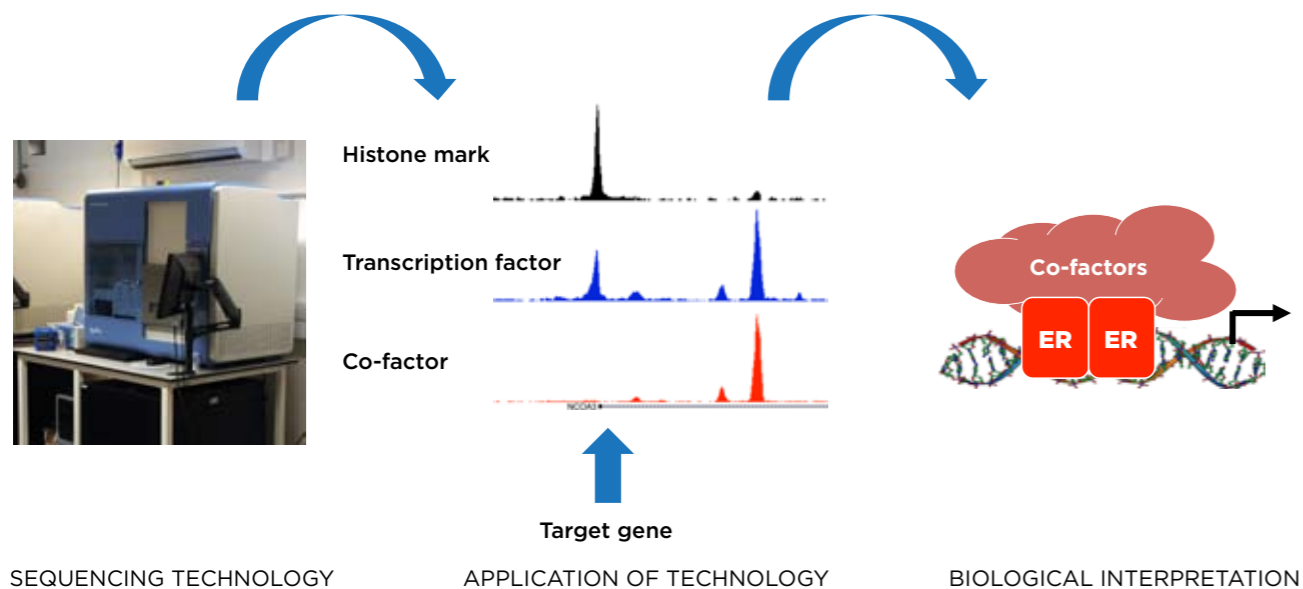
But of course it isn't that straightforward. It turns out (by using NGS coupled with nuclear run-on approaches) that a large fraction of the empty space within the genome is actually producing non-coding RNA transcripts, many of which are mediated by factors such as the ER. One would suspect that some of these non-coding RNAs must be doing something to the physiology of a cell. Given the huge quantity of data coming out of NGS applications, it's no surprise that we are now entirely dependent on having computational biologists to make sense of the information.

With new technological capabilities come new problems. NGS has provided an unprecedented and, at times, overwhelming insight into how the genome responds to and contributes to our specific diseases. We can either stick our head in the sand and pretend we don't know about this complexity (which, on some mornings, I support) or we need to tackle this rapidly increasing wealth of genomic information.

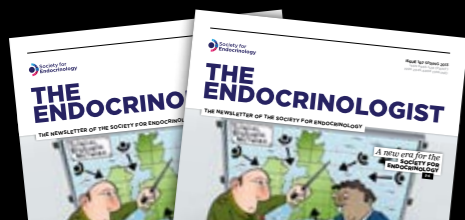
Will we learn something useful from all of these sequencing-based approaches? Absolutely, but it requires the biologists to pick apart the massive quantity of data, finding interesting non-coding RNAs, transcription factor binding events, chromatin loops or other regulatory elements to study in isolation and in great detail, and possibly for significant chunks of their careers.

JASON S CARROLL  
CANCER RESEARCH UK AND DEPARTMENT OF ONCOLOGY,  
UNIVERSITY OF CAMBRIDGE

NGS technology is evolving rapidly. Our current machines can read 200 million short pieces of DNA in one go. By coupling this sequencing capacity with other techniques, we can explore things such as global transcription factor mapping. Interpretation of these genomic datasets can teach us about the underlying biological properties of our favourite factors. In the example shown, the ER is studied in parallel with one of its associated cofactors and histone marks. Histone marks help define active versus inactive regions of the genome that correlate with gene expression potential.



## NEW LOOK FOR THE ENDOCRINOLOGIST



As you will have noticed, in line with our new identity, The Endocrinologist has undergone a revamp of its own. Not only has the title been adapted to our new house style, but the overall look and feel of our new design has given the newsletter a fresh, vibrant look that reflects our guiding principles (**Engage, Support, Advance**). We will continue to work hard at providing you with the most up to date editorial content, topical discussions and debates in endocrinology and the wider medical and scientific communities that matter most to you. Let us know your thoughts and views on this.

Email us at [info@endocrinology.org](mailto:info@endocrinology.org), Facebook or Tweet us. We look forward to hearing from you.

# HOT TOPICS



Society members have free access to the current content of *Journal of Endocrinology*, *Journal of Molecular Endocrinology*, *Endocrine-Related Cancer* and *Clinical Endocrinology* via [www.bioscialliance.org](http://www.bioscialliance.org). *Endocrine Connections* is an open access journal and as such is free to all.

## JOURNAL OF ENDOCRINOLOGY

### Testosterone improves adipose tissue function

Rabbits with diet-induced metabolic syndrome (MetS) are hypogonadal and show increased and dysfunctional visceral adipose tissue. Maneschi and colleagues studied the effect of *in vivo* testosterone dosing on MetS animals and found that it reduces visceral fat mass and improves adipose tissue function. Adipogenic capacity of visceral preadipocytes from testosterone-treated MetS rabbits was improved through a positive effect on their insulin sensitivity.

### GH improves spatial memory in rats

Grönbladhaff *et al.* report effects of GH on memory in intact rats pretreated with the anabolic androgenic steroid (AAS) nandrolone. GH had a significant positive effect on memory functions and increased *Igf1* gene expression in the hippocampus. It increased body weight gain and could attenuate the reduced body weight seen in nandrolone-treated animals. In conclusion, GH improves spatial memory in intact rats and can reverse certain effects induced by AAS.

## JOURNAL OF MOLECULAR ENDOCRINOLOGY

### Rosiglitazone and hepatic LRP1

Moon and co-workers hypothesised that thiazolidinediones such as rosiglitazone may increase hepatic LDL receptor-related protein 1 (LRP1) and the hepatic clearance of remnant lipoproteins. A diabetic condition including high glucose was shown to decrease hepatic LRP1 expression. Rosiglitazone increased LRP1 expression and function in HepG2 cells and the livers of diabetic rats. Decreased hepatic LRP1 in a diabetic condition may be associated with development of atherogenic dyslipidemia, and an increase in hepatic LRP1 by thiazolidinediones could help improve atherogenic lipid profiles in diabetic patients.

### 11 $\beta$ -HSD1 regulates BAT function

Liu *et al.* observed a remarkable decrease in BAT-specific gene expression in brown adipocytes when 11 $\beta$ -HSD1 was overexpressed, which was normalised by BVT.2733 (a selective inhibitor of 11 $\beta$ -HSD1) treatment. This indicates that 11 $\beta$ -HSD1 acts as a vital regulator of the expression of genes related to brown fat function, and as such may become a potential target in preventing obesity.

## ENDOCRINE-RELATED CANCER

### KLF5 in breast cancer

Takagi and colleagues immunolocalised Krüppel-like factor 5 (KLF5) to the nucleus of breast carcinoma cells, and demonstrated an association between KLF5 and the status of the androgen receptor. KLF5 was also associated with an increased risk of recurrence and a poor clinical outcome. This work suggests that KLF5 is an androgen-responsive gene in human breast cancer, plays an important role in progression, and may be of prognostic use.

### Increasing effectiveness of androgen deprivation

Mooso *et al.* showed that Filamin A (FlnA) nuclear localisation induced apoptosis in castration-resistant prostate cancer (CRPC) cells during androgen deprivation therapy (ADT). The natural product genistein combined polysaccharide (GCP) had a similar effect, by inducing FlnA cleavage and nuclear localisation. In a mouse model of prostate cancer recurrence, GCP, but not vehicle, impeded relapse following castration. These results demonstrate the efficacy of GCP in promoting FlnA nuclear localisation in prostate cancer.

## ENDOCRINE CONNECTIONS

### Inverse association between serum insulin and SHBG

Daka *et al.* found a significant inverse association between levels of sex hormone binding globulin (SHBG) and fasting serum insulin in both genders, independent of age and BMI. The associations remained when differences in fasting plasma glucose were taken into account. Subjects with type 1 diabetes exhibited higher levels of SHBG than those with type 2 diabetes and non-diabetic subjects. This suggests an inhibitory effect of insulin on liver SHBG production.

### HPA axis rhythms in end-stage renal disease

End-stage renal disease patients can display features of hypercortisolism, but are difficult to diagnose as having Cushing's syndrome. Raff & Trivedi investigated plasma and salivary cortisol in end-stage renal patients, finding a discernible circadian rhythm with a significantly higher nadir (at 1800-2400 h) compared with healthy controls.

## CLINICAL ENDOCRINOLOGY

### Medical therapy in Cushing's syndrome

Surgery is the treatment of choice for Cushing's syndrome; however, steroidogenesis inhibitors such as ketoconazole or metyrapone have been used preoperatively to lower circulating cortisol and reduce surgical risk. These agents have also been used after pituitary irradiation or unsuccessful surgery. In this retrospective study, Valassi *et al.* demonstrate that preoperative administration of ketoconazole, metyrapone or both normalise cortisol in more than half of Cushing's syndrome patients, although clinical improvement was not achieved in all.

### Maternal diet and epigenetics

Epidemiological studies have revealed an association between poor maternal diet and cardiometabolic disease risk in adult life. Suggested mechanisms include foetal glucocorticoid overexposure and reduced growth factor exposure. This study by Drake and colleagues found alterations in DNA methylation at genes involved in cortisol regulation, tissue glucocorticoid action, blood pressure and foetal growth, in a cohort of 34 individuals. This suggests a persistent epigenetic link between maternal diet, foetal growth, and adult cardiometabolic risk.

# A new option for patients with adrenal insufficiency



## Comparison of PLENADREN® (Hydrocortisone modified-release tablets) and current hydrocortisone therapy with normal daily serum cortisol levels

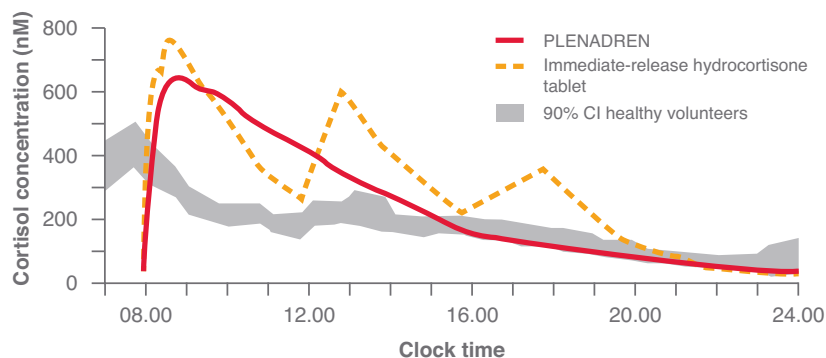


Figure derived from Johansson et al.<sup>1</sup> and healthy volunteer data based on Vgontzas et al.<sup>2</sup>

## PLENADREN compared to immediate release hydrocortisone TID:

- Is a once-daily, hydrocortisone modified-release tablet developed to better mimic natural circadian daytime cortisol release<sup>1</sup>
- Consists of an immediate release coating that provides physiological cortisol concentrations within 20 minutes (20 mg);<sup>3</sup> an extended release core provides a smooth cortisol serum profile over the day and a night-time cortisol-free interval<sup>1</sup>
- Resulted in 85% of patients participating in the 12-week open-label crossover study preferring PLENADREN<sup>1</sup>

### ABBREVIATED PRESCRIBING INFORMATION

Please refer to the Summary of Product Characteristics for full product information.

#### PLENADREN® ▼ (Hydrocortisone modified-release tablets) 5 mg and 20 mg

**Presentation:** Pink, round, convex tablets containing hydrocortisone 5 mg or white, round, convex tablets containing hydrocortisone 20 mg. **Indications:** Treatment of adrenal insufficiency in adults. **Dosage:** A common maintenance dose is 20–30 mg per day, given once daily in the morning. The lowest possible maintenance dose should be given. PLENADREN tablets should be taken orally with a glass of water on awakening, at least 30 minutes before food intake, preferably in an upright position and between 6.00 am and 8.00 am in the morning. Tablets should be swallowed whole. **Changing from conventional oral glucocorticoid treatment to PLENADREN** An identical total daily dose of PLENADREN may be given. Due to a lower bioavailability of the daily dose of PLENADREN compared to that of conventional hydrocortisone tablets given three times daily, clinical response needs to be monitored and further dose individualisation may be required. **Use in intercurrent illness** **Severe situations:** An increase in dose is immediately required and oral administration of hydrocortisone must be replaced with parenteral treatment. **Less severe situations:** The normal oral daily replacement dose must be increased temporarily; the total daily dose of PLENADREN should be increased by administering the maintenance dose twice or thrice daily with 832 hour intervals. **Children/adolescents under 18:** No data on safety and efficacy in subjects below the age of 18 are available. **Elderly patients:** Dose adjustment to a lower dose may be necessary in case of age-related low body weight. **Patients with renal or hepatic impairment:** In patients with severe impairment, dose adjustment may be required. **Contraindications:** Hypersensitivity to any of the components of the product. **Special warnings and precautions:** During acute adrenal insufficiency parenteral administration of hydrocortisone, in high doses, together with sodium chloride 9 mg/ml (0.9%) solution for injection must be given. Patients with concomitant adrenal insufficiency and retroviral infection need careful dose adjustment. Modified-release tablets are not recommended in patients with increased gastrointestinal motility due to the risk of impaired cortisol exposure. High dosages of hydrocortisone can cause elevation of blood pressure, salt and water-retention and increased excretion of potassium. Long term treatment with higher than physiological hydrocortisone doses can lead to clinical features

resembling Cushing's syndrome and thus result in an increased risk of cardiovascular morbidity and mortality. Old age and low body mass index are known risk factors for common adverse reactions of pharmacological doses of glucocorticoids. Patients with adrenal insufficiency on long-term glucocorticoid replacement therapy have been found to have reduced bone mineral density. Psychiatric adverse reactions may occur with systemic glucocorticoids. Risks may be higher when high doses are given. Patients with adrenal insufficiency should be monitored for hypothyroidism and hyperthyroidism as these conditions may markedly influence the exposure of administered hydrocortisone. **Pregnancy and lactation:** It is important to continue treatment with PLENADREN during pregnancy however the dose should be carefully monitored. PLENADREN can be used during breastfeeding. **Side effects:** Common: gastroenteritis, upper respiratory tract infection, viral infection, sedation, vertigo, dry eye, oesophagitis, nausea, upper abdominal pain, tooth erosion, pruritic rash, joint swelling, HDL decrease, weight increase. Very Common: fatigue. Other side effects are listed in the SmPC. **Legal category:** POM **Basic NHS price:** Bottle containing 50 x 20 mg tablets, £400.00. Bottle containing 50 x 5 mg tablets, £242.50. **MA Number:** EU/1/11/715/001-002 **Marketing Authorisation Holder:** ViroPharma SPRL, Rue Montoyer 47, B-1000 Brussels, Belgium **Date of revision of SmPC:** May 2012

Adverse events should be reported. Reporting forms and information can be found at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard)

Adverse events should also be reported to ViroPharma via email to [eu.medinfo@viropharma.com](mailto:eu.medinfo@viropharma.com) or via EU Med Info toll free, +800 8476 8476 / Belgium Tel +322 792 512

1. Johansson G et al. *J Clin Endocrinol Metab* 2012;97:473–481.
2. Vgontzas AN et al. *J Clin Endocrinol Metab* 2001;86:3787–3794.
3. Johansson G et al. *Eur J Endocrinol* 2009;161:119–130.

